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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/576,500	11/22/2006	Bernard Massie	2139-32US	4669

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EXAMINER	
SHEN, WU CHENG WINSTON	
ART UNIT	PAPER NUMBER
1632	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/576,500	MASSIE ET AL.	
	Examiner	Art Unit	
	WU-CHENG Winston SHEN	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27 and 30-32* is/are pending in the application.

4a) Of the above claim(s) *1-12,19-27 and 30-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 April 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on 07/18/2008 to the notice of non-compliance mailed on 06/26/2008 has been received and entered. The text of withdrawn claims 1-12, 19-27, and 30-32 have been included in the claim set filed on 07/18/2008. Claims 28, 29 and 33 are cancelled. Claims 1-27 and 30-32 are pending.

This application 10/576,500 is a 371 of PCT/CA04/01794 filed on 10/22/2004 which claims benefit of 60/514,532 filed on 10/24/2003.

Election/Restriction

1. Applicant's election of Group II, claims 13-18, drawn to a modified virus ablated of its natural receptors interactions with an unmodified or non-naturally occurring cell, said modified virus comprising a non- native polypeptide, said modified virus having an altered tropism conferred by said non-native peptide, and replicating only in cells that can interact with said non-native peptide, said virus being incapable of infecting a cell through a CAR-dependent entry pathway, further comprising retargeting adapter, which is a *de novo* designed E-coil or K-coil fused ligand, comprising: i) a binding moiety for binding the non-native polypeptide and ii) a further binding moiety of a receptor for retargeting said virus on cells expressing said receptor (See restriction requirement mailed on 04/22/2008), in the reply filed on 05/21/2008 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

With regard to election of species, Applicant elected adenovirus and claims 13-18 encompass the elected invention.

Claims 1-12, 19-27, and 30-32 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on June 16, 2006.

Claims 13-18 are currently under examination

Claim Rejection - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 13-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Curiel et al.** (US patent application publication 2002/0081280, publication date 06/27/2002, which became US patent 7,297,542, issued on 11/20/2007) in view of **Segal et al.** (Segal et al., US patent 7,211,250, issued 05/01/2007, filed on 07/16/2003).

Claim interpretation: The limitation recited in claim 17 "wherein said non-native polypeptide a *cleavage site* positioned in a location that enables a further binding moiety of a receptor to be added on the modified virus for retargeting said virus on cells expressing said

receptor" is interpreted as engineering the non-native polypeptide indirectly at DNA level in the context of an adenoviral vector, which in turn encode the non-native peptide.

With regard to the limitations of claim 13 of instant application, **Curiel et al.** teaches adenovirus vector containing a heterologous peptide epitope in the HI loop of the fiber knob to achieve CAR-independent gene transfer by adenovirus vector in clinically important contexts (for instance, gene therapy for treating cancers), modification of viral tropism via genetic alterations to the viral fiber protein by ablating the naïve tropism of the adenovirus via CAR receptor (See paragraph [0056], Curiel., 2002). Curiel et al. shows that incorporation of an Arg-Gly-Asp (RGD) containing peptide, such as CDCRGDCFC (which reads on a non-native polypeptide that render CAR-independent gene transfer by adenovirus vector as required by claim 13), in the HI loop of the fiber knob domain results in the ability of the virus to utilize an alternative receptor during the cell entry process (See paragraph [0142], Curiel., 2002).

With regard to the limitation recited in claim 16 pertaining to non-covalent physical forces selected from the group consisting of van der waals forces, electrostatic forces, stacking interactions, hydrogen bonding, and steric fit involved in protein-protein interactions, Curiel et al. teaches that the incorporation of large polypeptide ligands into the HI loop, which connects β-strands H and I involved in the formation of the cell binding site, may create a steric hindrance (which reads on steric fit being a physical force for adaptor binding to non-native polypeptide recited in claim 16), thereby preventing direct interaction of the fiber knob with CAR and resulting in elimination of endogenous tropism of the virus. This, in turn, would result in a new generation of truly retargeted adenoviral vectors, capable of cell-specific gene delivery exclusively via CAR-independent mechanisms (See paragraph [0190], Curiel et al., 2002).

With regard to the limitation recited in claim 17 pertaining to the presence of a cleavage site positioned in a location that enables a further binding moiety of a receptor to be added on the modified virus for retargeting said virus on cells expressing said receptor, Curiel et al. teaches that Ad5 genomic DNA in pTG3602 does not contain any unique restriction sites in the fiber gene, which limits its utility for modifications of fiber. Thus, to overcome this limitation, this plasmid was modified by inserting a unique *cleavage site* for the restriction endonuclease *Swa*I into the fiber gene. To this end, one of the two *Nde*I sites present in Ad5 DNA and localized 47 bp downstream from the fiber gene's 5' end was converted into *Swa*I site by insertion of a *Swa*I-linker (FIG. 5). The plasmid generated, pVK50, was then utilized for homologous recombination with the fragment of DNA containing the gene encoding fiber-FLAG flanked with viral DNA adjacent to the fiber gene in the Ad5 genome. As a result of this recombination, a plasmid, pVK300, containing a modified fiber gene in the context of the complete adenovirus genome was derived (See paragraph [0127], Curiel et al., 2002).

However, Curiel et al. does not teach (i) the modified virus further comprises a retargeting adaptor comprising a binding moiety of a receptor for retargeting said virus on cells expressing said receptor, as recited in claim 13, 17 and 18 and (ii) using at least one repeat of SEQ ID NO: 1 and at least one SEQ ID NO: 2 as a retargeting adaptor, as required in claims 14 and 15 of instant application.

Segal et al. teaches coil-coil heterodimer-subunit peptides, in either parallel or anti-parallel orientations, as a targeting moiety of a ligand that binds to cancer cell surface receptors for enhancing/retargeting the delivery of an therapeutic composition (for instance, an enzyme, or an vector encoding the enzyme) to cancer cells when the therapeutic composition is

administered to the subject (See lines 24-36, column 2, and lines 46-49, column 33, Segal et al. 2007). Segal et al. teaches exemplary coil-coil heterodimer-subunit peptide includes a positive charged K-coil peptide made of 7-amino acid, e.g., SEQ ID NO: 5 repeats (Lys-Val-Ser-Ala-Leu-Lys-Glu, which is identical to SEQ ID No: 2 of instant application), and a negative charged E-coil peptide made of 7-amino acid, e.g., SEQ ID NO: 6 repeats (Glu-Val-Ser-Ala-Leu-Glu-Lys, which is identical to SEQ ID No: 1 of instant application), and in one embodiment, the positive K-coil peptide is 35 amino acids in length (i.e. five repeats) and the negative charged E-coil is 35 amino acids in length (i.e. five repeats) (See Lines 53-60 column 33, Segal et al.). Segal et al. further teaches that coil-coil heterodimer-subunit peptide as a targeting moiety can be synthesized or derivatized after synthesis, and stabilizing ionic attraction or destabilizing ionic repulsion can be achieved by adjusting salt concentration (which reads on the limitation of physical forces including electrostatic forces and hydrogen bonding recited in claim 17 of instant application) (See lines 49-52, column 34, Segal et al., 2007).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to combine the teachings of Curiel et al. regarding ablating the naïve tropism of the adenovirus via CAR receptor by incorporation of a non-native polypeptide in a modified adenovirus, with the teachings of Segal et al. regarding coil-coil heterodimer-subunit peptides, in either parallel or anti-parallel orientations, as a targeting moiety of a ligand that binds to cancer cell surface receptors for enhancing/retargeting the delivery of an therapeutic composition to cancer cells to arrive at the claimed invention recited in claims 13-18.

One having ordinary skill in the art would have been motivated to combine the teachings of Curiel et al. with the teachings of Segal et al. because (i) Curiel et al. discloses that one

disadvantage to the use of recombinant adenoviruses for gene therapy is related to the virus' reliance on the presence of the coxsackievirus and adenovirus receptor (CAR) to achieve high levels of gene transfer, since in certain settings, this may result in sequestration of recombinant virions by nontarget, yet high CAR-expressing cells, whereas the true target cells, if low in CAR, are poorly transduced, and (ii) Segal et al. teaches that introduction of coil-coil heterodimer-subunit peptides formed by SEQ ID No:1 and SEQ ID No: 2 of instant application can form a targeting moiety of a ligand that binds to cancer cell surface receptors for enhancing/retargeting the delivery of an therapeutic composition, for instance, a vector encoding a therapeutic polypeptide, to cancer cells for gene therapy.

There would have been a reasonable expectation of success given (1) the successful demonstration of ablating the naïve tropism of the adenovirus via CAR receptor by incorporation of a non-native polypeptide, such as CDCRGDCFC, in a modified adenovirus by the teachings of Curiel et al., and (2) demonstration of introducing coil-coil heterodimer-subunit peptides formed by SEQ ID No:1 and SEQ ID No: 2 of instant application, by the teachings of Segal et al., can form a targeting moiety of a ligand that binds to cancer cell surface receptors for enhancing/retargeting the delivery of an therapeutic composition, a vector encoding a therapeutic polypeptide, to cancer cells for therapeutic purpose.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

3. Claims 13-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Nicklin et al.** (Ablating adenovirus type 5 fiber-CAR binding and HI loop insertion of the SIGYPLP peptide generate an endothelial cell-selective adenovirus. *Mol Ther.* 4(6):534-42, 2001; this

reference has been cited in the Restriction requirement mailed on 04/22/2008) in view of **Segal et al.** (Segal et al., US patent 7,211,250, issued 05/01/2007, filed on 07/16/2003).

Claim interpretation: The limitation recited in claim 17 "wherein said non-native polypeptide a *cleavage site* positioned in a location that enables a further binding moiety of a receptor to be added on the modified virus for retargeting said virus on cells expressing said receptor" is interpreted as engineering the non-native polypeptide indirectly at DNA level in the context of an adenoviral vector, which in turn encode the non-native peptide.

With regard to the limitations of claim 13 of instant application, **Nicklin et al.** generated genetically modified Ad fiber proteins with selective endothelial cells (EC) tropism by engineering peptides into the HI loop of the Ad fiber that ablates adenovirus type 5 fiber-CAR binding. Nicklin et al. taught that introduction of SIGYPLP (which reads on a non-native polypeptide recited in claim 13) enhanced vascular endothelial cells (EC) selectivity (which reads on altered tropism). Nicklin et al. demonstrated that combining fiber mutations that block CAR binding (de-targeting) with SIGYPLP insertion (re-targeting) generated a novel Ad vector, AdKO1SIG, in a single component system. The AdKO1SIG taught by Nicklin et al. demonstrated efficient and selective tropism for EC compared with control Ad vectors (See abstract, Nicklin et al., 2001).

With regard to the limitation recited in claim 17 pertaining to the presence of a cleavage site positioned in a location that enables a further binding moiety of a receptor to be added on the modified virus for retargeting said virus on cells expressing said receptor, Nicklin et al. teaches the cloning by the overlapping oligonucleotides encoding the sequence SIGYPLP into the BspE1

site of pDV111 vector, which in turn is cloned into adenovirus AdKO1SIG with linker sequences (See left column page 541, Nicklin et al., 2001).

However, Nicklin et al. does not teach (i) the modified virus further comprises a retargeting adaptor comprising a binding moiety of a receptor for retargeting said virus on cells expressing said receptor, as recited in claim 13, 17 and 18 and (ii) using at least one repeat of SEQ ID NO: 1 and at least one SEQ ID NO: 2 as a retargeting adaptor, as required in claims 14 and 15 of instant application.

Segal et al. teaches coil-coil heterodimer-subunit peptides, in either parallel or anti-parallel orientations, as a targeting moiety of a ligand that binds to cancer cell surface receptors for enhancing/retargeting the delivery of an therapeutic composition (for instance, an enzyme, or an vector encoding the enzyme) to cancer cells, when the therapeutic composition is administered to the subject (See lines 24-36, column 2, and lines 46-49, column 33, Segal et al. 2007). Segal et al. teaches exemplary coil-coil heterodimer-subunit peptide includes a positive charged K-coil peptide made of 7-amino acid, e.g., SEQ ID NO: 5 repeats (Lys-Val-Ser-Ala-Leu-Lys-Glu, which is identical to SEQ ID No: 2 of instant application), and a negative charged E-coil peptide made of 7-amino acid, e.g., SEQ ID NO: 6 repeats (Glu-Val-Ser-Ala-Leu-Glu-Lys, which is identical to SEQ ID No: 1 of instant application), and in one embodiment, the positive K-coil peptide is 35 amino acids in length (i.e. five repeats) and the negative charged E-coil is 35 amino acids in length (i.e. five repeats) (See Lines 53-60 column 33, Segal et al.). Segal et al. further teaches that coil-coil heterodimer-subunit peptide as a targeting moiety of a ligand can be synthesized or derivatized after synthesis, and stabilizing ionic attraction or destabilizing ionic repulsion for stable formation of coil-coil heterodimer peptides in the context

of a ligand, which recognized by a cell surface receptor, can be achieved by adjusting salt concentration (which reads on the limitation of physical forces including electrostatic forces and hydrogen bonding recited in claim 17 of instant application) (See lines 49-52, column 34, Segal et al., 2007).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to combine the teachings of Nicklin et al. regarding ablating the naïve tropism of the adenovirus via CAR receptor by incorporation of a non-native polypeptide in a modified adenovirus, with the teachings of Segal et al. regarding coil-coil heterodimer-subunit peptides, in either parallel or anti-parallel orientations, as a targeting moiety of a ligand that binds to cancer cell surface receptors for enhancing/retargeting the delivery of an therapeutic composition to cancer cells to arrive at the claimed invention recited in claims 13-18.

One having ordinary skill in the art would have been motivated to combine the teachings of Nicklin et al. with the teachings of Segal et al. because (i) Nicklin et al. discloses recombinant adenovirus type 5 based vectors (Ad) have been widely used for gene delivery to the vasculature, however, Ads transduce many cell types, due to the wide distribution of the Ad5 receptor, the coxsackievirus-adenovirusreceptor (CAR), and strategies for retargeting Ad have included insertion of heterologous sequences into the fiber knob, or by coating Ad vectors with polymers linked to targeting moiety (See Introduction, left column, page 534, Nicklin et al., 2001), and (ii) Segal et al. teaches that introduction of coil-coil heterodimer-subunit peptides formed by SEQ ID No:1 and SEQ ID No: 2 of instant application, by the teachings of Segal et al., can form a targeting moiety of a ligand that binds to cancer cell surface receptors for enhancing/retargeting

the delivery of an therapeutic composition, for instance, a vector encoding a therapeutic polypeptide, to cancer cells for gene therapy.

There would have been a reasonable expectation of success given (1) the successful demonstration of ablating the naïve tropism of the adenovirus via CAR receptor by incorporation of a non-native polypeptide, such as SIGYPLP, in a modified adenovirus by the teachings of Nicklin et al., and (2) introduction of coil-coil heterodimer-subunit peptides formed by SEQ ID No:1 and SEQ ID No: 2 of instant application can form a targeting moiety of a ligand that binds to cancer cell surface receptors for enhancing/retargeting the delivery of an therapeutic composition, a vector encoding a therapeutic polypeptide, to cancer cells for therapeutic purpose.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Conclusion

4. No claim is allowed.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent

examiner, Peter Paras, Jr. can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Wu-Cheng Winston Shen/

Patent Examiner
Art Unit 1632